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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/525,549

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John P. Wikswo

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EXAMINER

BOWERS, NATHAN ANDREW

ART UNIT

PAPER NUMBER

1797

MAIL DATE

DELIVERY MODE

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/525,549	<b>Applicant(s)</b> WIKSWO ET AL.	
	<b>Examiner</b> NATHAN A. BOWERS	<b>Art Unit</b> 1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 24 October 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-65 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-65 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 February 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>080307, 030607, 092606, 071706, 041206</u> .                  | 6) <input type="checkbox"/> Other: _____                          |



## **DETAILED ACTION**

### ***Priority***

The disclosure of the prior-filed application, Application No. 60/406278, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Application No. 60/406278 does not describe the use of a barrier to divide a chamber into a first subchamber and a second subchamber, wherein the barrier has a porosity to allow the permeation of a predetermined cell type.

Accordingly, claims requiring this limitation are not awarded the priority date established by Application No. 60/406278.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1) Claims 1-9, 14-16, 60, 61, 64 and 65 are rejected under 35 U.S.C. 102(e) as being anticipated by Thomas (US 20060194273).

With respect to claims 1, 15, 16, 60, 61, 64 and 65, Thomas discloses a bioreactor for cultivating living cells in a liquid medium comprising a first substrate

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(Figure 1b:18) having first and second opposing surfaces and a chamber (Figure 1a:2) formed therebetween. This is disclosed in paragraphs [0027] and [0028]. Paragraph [0030] states that a barrier (Figure 3:15) is used to divide the chamber in a first subchamber and a second subchamber. Thomas states that the barrier has a porosity of 5 to 50 microns. Cells comprising a diameter greater than the chosen porosity will inherently be permitted movement through the barrier gaps, whereas cells comprising a diameter less than the chosen porosity will be allowed to permeate through the gaps.

With respect to claim 2, Thomas discloses the bioreactor set forth in claim 1. As noted above, the first subchamber is adapted for receiving cells of all diameters, whereas the second subchamber is adapted for receiving cells only of diameters smaller than the barrier gaps.

With respect to claims 3-5, Thomas discloses the bioreactor set forth in claim 2. The Thomas bioreactor is considered to be fully capable of accommodating any type of microorganism including bacteria and protozoa.

With respect to claims 6 and 7, Thomas discloses the bioreactor set forth in claim 1 wherein biocompatible coatings are used to enhance cell adhesion. This is disclosed in paragraphs [0040] and [0042].

With respect to claims 8 and 9, Thomas discloses the bioreactor set forth in claim 1 wherein an input port (Figure 1b:9) and an input transfer channel (Figure 1a:1) are formed in the substrate and provided in fluid communication with the first subchamber. This is disclosed in paragraph [0027]. Furthermore, an outlet port (Figure 1b:10) and an

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outlet transfer channel (Figure 1a:5) are provided in communication with the second subchamber.

With respect to claim 14, Thomas discloses the bioreactor set forth in claim 1 wherein the first substrate is formed from a transparent plastic or polymeric material. This is described in paragraph [0032].

2) Claims 1-5, 8-17, 33-38, 41-48 and 57-65 are rejected under 35 U.S.C. 102(e) as being anticipated by Kanegasaki (US 20030003571).

With respect to claim 1, 15, 16, 33, 45-48 and 57-65, Kanegasaki discloses a bioreactor for cultivating cells in a liquid medium comprising a first substrate (Figure 5:7) having first and second surfaces defining a chamber therebetween. A barrier comprising a channel (Figure 5:1) and a plurality of protrusions (Figure 5:6) serve to divide the chamber into a first subchamber (Figure 5:2A) and a second subchamber (Figure 5:2B). This is disclosed in paragraphs [0084], [0085] and [0095]. Paragraph [0097] states that the protrusions and grooves formed within the channels are varied in order to control the diffusion of a particular cell type between the subchambers. Paragraph [0121] states that the gaps of the barrier range from 3 to 50 microns. Figure 12 and paragraph [0112] describe another configuration in which first and second barriers (1) are positioned so as to form a central chamber (2A), an intermediate chamber (2B), and an outer chamber (2C).

With respect to claims 2 and 34, Kanegasaki discloses the bioreactor set forth in claims 1 and 33. As noted above, the barriers located between the first and second

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subchambers are adapted for allowing the perfusion of certain cell types while restricting the movement of certain cell types.

With respect to claims 3-5 and 35-38, Kanegasaki discloses the bioreactor set forth in claims 2 and 33. The Kanegasaki bioreactor is considered to be fully capable of accommodating any type of microorganism including bacteria, protozoa, tumor cells, endothelial cells, and normal tissue cells.

With respect to claims 8 and 9, Kanegasaki discloses the bioreactor set forth in claim 1 wherein an input port (Figure 3:3Aa) and an input transfer channel are formed in the substrate and provided in fluid communication with the first subchamber. Furthermore, an outlet port (Figure 3:3Ba) and an outlet transfer channel are provided in communication with the second subchamber.

With respect to claims 10 and 11, Kanegasaki discloses the bioreactor set forth in claim 9 wherein at least one auxiliary port and channel are provided in fluid communication with the input and outlet ports. Kanegasaki teaches that additional ports (Figure 3:4Ba and Figure 3:4Aa) are used in conjunction with inlet (Figure 3:3Aa) and outlet (Figure 3:3Ba) ports, so as to supply extra reagents to the subchambers.

With respect to claims 12 and 13, Kanegasaki discloses the bioreactor set forth in claim 11 wherein a second substrate (Figure 6:9) is positioned adjacent to a first surface of the first substrate (Figure 6:7). The second substrate comprises a plurality of connection channels (Figure 6:3A, 4A, 4B, 3B) that are aligned with the inlet/outlet ports of the first substrate.

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With respect to claims 14 and 44, Kanegasaki discloses the bioreactor set forth in claims 1 and 33 wherein the first substrate is formed from silicon. This is described in paragraph [0154].

With respect to claim 17, Kanegasaki discloses the bioreactor set forth in claim 1 wherein a third substrate (Figure 6:8) is provided in communication with a second surface of the first substrate (Figure 6:7).

With respect to claims 41-43, Kanegasaki discloses the bioreactor set forth in claim 33 wherein inlet and outlet ports (Figure 12:3a, 4a) are provided for each of the external, central, and intermediate chambers.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.



This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3) Claims 18-24 and 49-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kanegasaki (US 20030003571) as applied to claim 17, and further in view of Lynes (US 20020086280).

With respect to claims 18-22 and 49-52, Kanegasaki discloses the apparatus set forth in claim 17 as set forth in the 35 U.S.C. 102 rejection above, however does not expressly disclose that the third substrate includes a means for electrochemical measurements.

Lynes discloses a substrate (Figure 1:58) designed to monitor cell movement in response to chemotactic factors. Paragraphs [0018] and [0019] indicate that a plurality of individually addressable working electrodes (Figure 1:10) and counter electrodes are arrayed upon the substrate so as to measure changes in impedance, resistance or capacitance that result from the motion of cells (Figure 1:54). Lynes further describes the use of at least one reference electrode. Figure 2 indicates that a plurality of edge

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connector pads and electrically conductive leads are in communication with each electrode. The effect of a certain analyte is determined by monitoring cell behavior upon the introduction of the analyte into the culture solution.

Kanegasaki and Lynes are analogous art because they are from the same field of endeavor regarding cell migration detection systems.

At the time of the invention, it would have been obvious to provide a third substrate in the system of Kanegasaki with a plurality of electrode capable of detecting cell movement. This would allow for a second means to determine cell behavior in addition to simple visual observation. Generally speaking, automated detection using impedance measurements is often times superior to visual observation, which is difficult and laborious. Paragraph [0017] of Lynes teaches that electrical detection using a patterned array of electrodes offers a rapid, automated and multiplexed analysis of cell movement and factors capable of affecting such movement.

With respect to claims 23 and 24, Kanegasaki and Lynes disclose the apparatus set forth in claim 17. Kanegasaki additionally describes the use of silicon substrates in paragraph [0154].

With respect to claims 53-56, Kanegasaki and Lynes disclose the apparatus set forth in claim 52. The plurality of electrodes disclosed by Lynes are fully capable of being subdivided into any number of subgroups. The creation of second and third electrode groups would not require any change in the structure of the device, but would

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merely require a change in the experiment protocol. Altering the controller program does not result in a structurally significant limitation in an apparatus claim, but rather represents an intended use.

4) Claims 25-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kanegasaki (US 20030003571) as applied to claim 1, and further in view of Allen (US 20040142409).

Kanegasaki discloses the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 102 rejection above. Although Kanegasaki discloses in paragraphs [0163]-[0165] an optical system for the interrogation of motile cells, Kanegasaki does not indicate that the optical sensors and light sources are provided on a substrate above the first substrate.

Allen discloses a detection system for monitoring the movement and presence of a cell (Figure 1:56) in a solution. An upper substrate (Figure 1:25) is provided above the base substrate (Figure 1:10), and serves to house a light source (Figure 1:30) and a photodetector (Figure 1:40). This is described in paragraphs [0033]-[0035].

Kanegasaki and Allen are analogous art because they are from the same field of endeavor regarding optical means for monitoring cell movement in a microfluidic system.

At the time of the invention, it would have been obvious to provide the Kanegasaki device with an additional substrate capable of holding a plurality of optical sensors, LED light sources and other optical detection means well known in the art. By

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arranging all critical optical components on an independent substrate, the overall apparatus would be characterized by a modular construction that would allow one to add and remove the optical devices with greater ease. As evidenced by Allen, it is well known in the art to form important detection means integral with a substrate formed above a culture chamber.

5) Claims 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kanegasaki (US 20030003571) as applied to claim 33, and further in view of Thomas (US 20060194273).

Kanegasaki discloses the apparatus set forth in claim 33 as set forth in the 35 U.S.C. 102 rejection above, however does not expressly disclose the use of cell adhesion coatings.

Thomas discloses the bioreactor as previously described above. In paragraphs [0040] and [0042], Thomas teaches that biocompatible coatings are applied to the surfaces of the cell chamber in order to promote cell adhesion.

Kanegasaki and Thomas are analogous art because they are from the same field of endeavor regarding microfluidic bioreactors.

At the time of the invention, it would have been obvious to utilize the adhesion promoting coatings disclosed by Thomas in the apparatus set forth by Kanegasaki. In paragraph [0160], Kanegasaki teaches that materials that encourage cell adhesion to substrate surfaces are beneficial. One of ordinary skill in the art would have recognized that the application of a coating to the substrate of Kanegasaki would have required

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only minor structural alterations, and would be completed in a predictable manner while yielding predictable results.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 8-11, 14-16, 33-38, 41-48 and 60-65 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 44-49 and 58-65 of copending Application No. 10/525559. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are generic to those of copending Application No. 10/525559. The claims of copending Application No. 10/525559 indicate that barriers are formed from first and second filters, as well as an array of

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posts. One of ordinary skill in the art would recognize that filters and posts in a cell culture system would serve to allow the passage of certain types of cells while restricting the movement of larger cells.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-65 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-77 of copending Application No. 10/525538. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are generic to those of copending Application No. 10/525538. The claims of copending Application No. 10/525538 include limitations that indicate that at least one barrier is formed in order to separate different types of cells (see claims 8 and 56). The independent claims of copending Application No. 10/525538 include additional limitations absent from the instant application that further describe the configuration of the chambers and channels within the bioreactor.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Conclusion***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The Rodgers (US 20050032204) discloses the state of the art

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regarding the use of barriers in a cell culture system (see Figure 10). The Sugihara (US 6890762) reference teaches the state of the art regarding microelectrode arrays capable of monitoring cell position.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NATHAN A. BOWERS whose telephone number is (571)272-8613. The examiner can normally be reached on Monday-Friday 7 AM to 4 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/William H. Beisner/  
Primary Examiner, Art Unit 1797

/Nathan A Bowers/  
Examiner, Art Unit 1797